REMARKS

The Office Action objected to several informalities in the specification.

The specification has been amended to correct items A, B and C. Applicants have been unable to locate item D.

The Office Action objected to claims 4 and 10 as being improper because they fail to indent each element of the claims. These claims have been amended to address this objection.

The Office Action rejected claims 4-6 and 10 under 35 U.S.C. §112, second paragraph as being indefinite. Claims 4 and 10 have been amended to address this rejection and claims 5 and 6 have been cancelled. Accordingly, this rejection should be withdrawn.

The Office Action rejected claim 6 under 35 U.S.C. §101 and §112, first paragraph, as lacking utility.

Claim 6 has been cancelled. Therefore, these rejections are moot.

The Office Action rejected claims 4, 5 and 10 under 35 U.S.C. §112, first paragraph, as not enabled in their entire scope.

The Office Action alleges that the present application only discloses the effect of ET_A blockers in delaying restenosis; there is no disclosure on the effect of selective ET_B blockers on restenosis. Furthermore, the Office Action alleges that Münter et al. teach that selective ET_B blockade has never seriously been considered as a therapeutic option and that ET_A and ET_B antagonists are mutually exclusive in that they reach opposing endpoints (section 2.1, page 4, left column, second paragraph). Therefore, according to the Office

Action the use of ET_B antagonist as a therapeutic agent is unpredictable; consequently, claims 4, 5 and 10 relating to any endothelin blocker are thus not enabling in their entire scope.

Applicants disagree with this conclusion.

In addition to stating that selective ET_B receptor blockade has never seriously been considered as a therapeutic option, Münter et al. also states that the ET receptor subtypes cannot be considered as isolated entities - a cross-talk between ET_A and ET_B receptors with consequences not totally understood so far has been described (section 2.1, page 4, left column, second paragraph). Furthermore, nearly all preclinical and clinical studies have shown that selective ET_A and non-selective ET_A/ET_B receptor blockers are similarly effective in different cardiovascular disease states (section 2.1, page 4, right column, second paragraph). The preclinical and clinical results clearly dispute the allegation that ET_A and ET_B antagonists are mutually exclusive in that they reach opposing endpoints. Moreover, according to Münter et al., the vasodilator component of ET_B receptors is much more pronounced than the constrictive action in normally functioning vascular endothelium (section 1, page 3, second paragraph). It is, however, not clear what the predominant function of ET_B is in injured vascular endothelium as in various cardiovascular disorders, in particular restenosis after PTCA. Therefore, applicants submit that there is not a sufficient and well-founded reason to suspect that ET_B blockade would not result in a beneficial clinical outcome.

The Office Action alleges that the specification of the present application lacks examples of how a pharmaceutical composition or a trade package comprising an ET

receptor blocker and an $\alpha_v\beta_3$ integrin receptor antagonist could be used to treat or prevent any and every disease. Therefore, according to the Office Action, the intended uses of the pharmaceutical composition of claims 4 and 5 or the trade package of claim 10 are fraught with uncertainties; the claimed invention cannot be practiced by a person skilled in the art without undue experimentation.

Claims 4 and 10 are limited to the treatment and prevention of cardiovascular diseases. As noted above, this is supported by the specification and the literature. Accordingly, this rejection should be withdrawn.

The Office Action rejected claims 4-6 under 35 U.S.C. §103(a) as being unpatentable over Kirchengast et al. In view of Srivatsa et al. The Office Action states that Kirchengast et al. disclose that ET receptor blockers are able to reduce restenosis and Srivatsa et al. disclose that $\alpha_v\beta_3$ integrin receptor blockers are capable of reducing restenosis. Therefore, according to the Office Action, it is obvious to a person skilled in the art to combine two compositions, each of which is taught by the prior art to be useful for the same purpose. Furthermore, the Office Action alleges that a person skilled in the art would have a reasonable expectation of success in combining the two compositions in the absence of evidence to the contrary.

The combination of the present application is not obvious to a person skilled in the art for the following reasons:

(1) Selection of one particular combination of two approaches from a large number of possibilities without any guidance was not obvious.

As early as 1995 a large number of small molecule approaches to the prevention

of restenosis were well-known in the art (see Reference U). The approaches listed in Reference U were by no means exhaustive as the use of $\alpha_V\beta_3$ integrin receptor inhibitors for reducing restenosis was not mentioned even though supporting experimental evidence had been published earlier (references 19, 22 and 23 of Reference V). Therefore, it can be said that a very large number of small molecule approaches to the prevention of restenosis were known at the priority date of the present application; the number of possible combinations of these known approaches would be even higher.

Since the precise molecular processes responsible for pathological restenosis were not well understood at the time (Reference W, page 550, right column, second paragraph) and there were mixed results for various small molecule approaches (Reference U), it would not have been obvious to a person skilled in the art which particular approach or what exact combination of approaches to pursue. Moreover, none of the prior art documents, N-Q and U-W, provided any indication that the particular combination of an ET blocker with an $\alpha_V\beta_3$ integrin receptor antagonist may be used for the treatment of restenosis.

Therefore, even though, theoretically, a person skilled in the art could combine two compositions each of which is taught by the prior art to be useful for the same purpose, in reality, there is no reason to believe that the person skilled in the art would have chosen the particular combination of an ET blocker and an $\alpha_V\beta_3$ integrin receptor antagonist from the extremely large number of possibilities.

(2) The lack of similar disclosure indicates the non-obviousness of the present combination.

The potential use of an ET blocker for treating cardiovascular diseases was known as early as 1994 if not earlier (see references 55, 56, 57 of Reference U). The potential use of an $\alpha_V\beta_3$ integrin antagonist for treating restenosis was also known as early as 1994 (see references 19, 22 and 23 of Reference V). Five years lapsed between 1994 and the priority date of the present application without any disclosure of the use of an ET blocker in combination with an $\alpha_V\beta_3$ integrin receptor antagonist for the treatment of restenosis.

Given the fact that cardiovascular disease is the number one disease of developed countries and that about a quarter of a million patients per year suffered from restenosis following PTCA in the 1990s (Reference W, left column, first paragraph), it can be said that there was a great need for effective treatment(s) of restenosis. Furthermore, given the fact that the cardiovascular field is one of the most researched fields in modern biomedical sciences, the absence of any disclosure similar to the present application in the five-year period can only be interpreted to mean that the combination of the present application was not obvious to a person skilled in the art.

For the above reasons, the subject matter of claim 4 is not obvious to a person skilled in the art. Therefore, this rejection should be withdrawn.

The Office Action rejected claim 10 under 35 U.S.C. §103(a) as being unpatentable over Kirchengast et al. in view of Srivatsa et al. and U.S. Patent No. 4,761,406. According to the Office Action, the trade package of claim 10 which comprises the pharmaceutical composition of claim 4 is not patentable because the composition is not patentable and the use of a trade package is not patentable in view of US Patent No. 4,761,406.

Applicants disagree with the Examiner for the reasons detailed above. The

combination of an ET blocker and an $\alpha_v\beta_3$ integrin receptor antagonist is patentable as discussed above. Consequently, a trade package comprising said combination of agents is patentable and this rejection should be withdrawn.

Favorable consideration and allowance of claims 4 and 10 as presently amended is requested.

Respectfully submitted,

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